

Exhibit A

U.S. Patent No. 7,741,080 (first page)



US007741080B2

(12) **United States Patent**
Kadowaki et al.(10) **Patent No.:** **US 7,741,080 B2**
(45) **Date of Patent:** **Jun. 22, 2010**(54) **ADIPONECTIN EXPRESSION-INDUCING AGENTS AND USES THEREOF**

WO WO 2005/094866 10/2005

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Toshimasa Yamauchi, Tokyo (JP);
Shoko Kitajima, Tokyo (JP); **Yusuke Ito**, Saitama (JP)(73) Assignees: **Nissan Chemical Industries, Ltd.**,
Tokyo (JP); **Toudai TLO, Ltd.**, Tokyo
(JP)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 285 days.(21) Appl. No.: **10/594,969**(22) PCT Filed: **Mar. 31, 2005**(86) PCT No.: **PCT/JP2005/006357**§ 371 (c)(1),
(2), (4) Date: **Mar. 14, 2007**(87) PCT Pub. No.: **WO2005/094866**PCT Pub. Date: **Oct. 13, 2005**(65) **Prior Publication Data**

US 2007/0203061 A1 Aug. 30, 2007

Related U.S. Application Data(60) Provisional application No. 60/557,708, filed on Mar.
31, 2004.(51) **Int. Cl.****C12P 19/34** (2006.01)**C12N 15/00** (2006.01)**C07H 21/04** (2006.01)(52) **U.S. Cl.** **435/91.1; 536/23.1; 435/320.1;**
435/455; 435/325(58) **Field of Classification Search** None
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**6,582,909 B1 * 6/2003 Bougueler et al. 435/6
7,365,170 B2 * 4/2008 Cooper et al. 530/399
2004/0241802 A1 12/2004 Kadowaki et al.**FOREIGN PATENT DOCUMENTS**EP 1 577 388 9/2005
WO WO 00/26363 5/2000
WO WO 01/32868 5/2001
WO WO /02/101075 A2 * 12/2002
WO WO 2004/058970 7/2004
WO WO 2004/061108 7/2004
WO WO 2004/078741 9/2004**OTHER PUBLICATIONS**Post et al., Gene therapy versus protein-based therapy: a matter of
pharmacokinetics. *Drug Discovery Today*, 6, 769-770, 2001.*Berg et al. *Nat Med.* (Aug. 2001) 7(8): 947-53.Friedman *Nature* (Apr. 6, 2000) 404(6778): 632-4.Hotamisligil et al. *Science* (Jan. 1, 1993) 259(5091): 87-91.Hotta et al. *Arterioscler Thromb Vasc Biol.* (Jun. 2000) 20(6): 1595-9.Hu et al. *J Biol Chem.* (May 3, 1996) 271(18): 10697-703.Kersten et al. *Nature.* (May 25, 2000) 405(6785): 421-4.Kubota et al. *J Biol Chem.* (Jul. 19, 2002) 277(29): 25863-6.Maeda et al. *Biochem Biophys Res Commun.* (Apr. 16, 1996) 221(2):
286-9.Maeda et al. *Nat Med.* (Jul. 2002) 8(7): 731-7.Matsuda et al. *J Biol Chem.* (Oct. 4, 2002) 277(40): 37487-91.Nakano et al. *J Biochem (Tokyo)* (Oct. 1996) 120(4): 803-12.Okamoto et al. *Circulation.* (Nov. 26, 2002) 106(22): 2767-70.Ouchi et al. *Circulation.* (Feb. 27, 2001) 103(8): 1057-63.Scheer et al. *Embo J.* (Jul. 15, 1996) 15(14): 3566-78.Scherer et al. *J Biol Chem.* (Nov. 10, 1995) 270(45): 26746-9.Shimoura et al. *Nat Med.* (Jul. 1996) 2(7): 800-3.Shulman *J Clin Invest.* (Jul. 2000) 106(2): 171-6.Spiegelman et al. *Cell* (Nov. 1, 1996) 87(3): 377-89.Steppan et al. *Nature* (Jan. 18, 2001) 409(6818): 307-12.Tomas et al. *Proc Natl Acad Sci USA.* (Dec. 10, 2002) 99(25):
16309-13.

(Continued)

Primary Examiner—Christine J Saoud*Assistant Examiner*—Elly-Gerald Stoica(74) *Attorney, Agent, or Firm*—Hunton & Williams LLP(57) **ABSTRACT**

The present invention provides adiponectin expression-inducing agents, and therapeutic agents using the same for obesity and obesity-related diseases such as cardiovascular diseases or metabolic diseases, as well as methods of searching for adiponectin expression-inducing agents.

KLF9, which can bind to the 32-bp fragment of position -188 to position -157 from the adiponectin expression start site, was demonstrated to enhance adiponectin promoter activity. Therefore, the present invention uses KLF9 as an adiponectin expression-inducing agent, and suggests that KLF9 replenishment therapy is useful for preventing and/or treating obesity or obesity-related diseases including metabolic diseases such as insulin resistance and type II diabetes, and cardiovascular diseases.

9 Claims, 11 Drawing Sheets

Exhibit B
Transmittal Sheet with USPTO date stamp

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371		68600.000002 U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 10/594969
INTERNATIONAL APPLICATION NO. PCT/JP2005/006357	INTERNATIONAL FILING DATE March 31, 2005	PRIORITY DATE CLAIMED March 31, 2004
TITLE OF INVENTION ADIPONECTIN EXPRESSION-INDUCING AGENTS AND USES THEREOF		
APPLICANT(S) FOR DO/EO/US Takashi KADOWAKI Toshimasa YAMAUCHI Shoko KITAJIMA Yusuke ITO		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. <input checked="" type="checkbox"/> The US has been elected (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input checked="" type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input checked="" type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> A copy of the oath or declaration of the inventor(s) as filed in the PCT Request (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).		
Items 11 to 20 below concern document(s) or information included:		
11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An Assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A Preliminary Amendment. 14. <input checked="" type="checkbox"/> An Application Data Sheet under 37 CFR 1.76. 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A power of attorney and/or change of address letter. 17. <input checked="" type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 37 CFR 1.821-1.825. 18. <input type="checkbox"/> A second copy of the published International Application under 35 U.S.C. 154(d)(4). 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 20. <input type="checkbox"/> Other items or information:		

IAP2 Rec'd PCT/PTO 29 SEP 2006

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.7) 10/594969		INTERNATIONAL APPLICATION NO. PCT/JP2005/006357		ATTORNEY'S DOCKET NUMBER 68600.000002	
The following fees have been submitted:				CALCULATIONS	PTO USE
21.	<input checked="" type="checkbox"/> Basic National Fee (37 CFR 1.492(a))	\$ 300.00		\$ 300.00	
22.	<input checked="" type="checkbox"/> Examination Fee (37 CFR 1.492(c))				
If the written opinion prepared by ISA/US or the International Preliminary Examination Report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) \$ 0.00				\$ 200.00	
All other situations \$ 200.00					
23.	<input checked="" type="checkbox"/> Search Fee (37 CFR 1.492(b))				
If the written opinion of the ISA/US or the International Preliminary Examination Report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) \$ 0.00					
Search Fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority \$ 100.00				\$ 400.00	
International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB \$ 400.00					
All other situations \$ 500.00					
TOTAL OF ABOVE CALCULATIONS =				\$ 900.00	
<input checked="" type="checkbox"/> Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) or computer program listing filed in an electronic medium) (37 CFR 1.492(j)). The fee is \$250.00 for each additional 50 sheets of paper or fraction					
Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round up to a whole number)	RATE		
41- 100	0 /50	0	x \$250.00	\$ 0.00	
Surcharge of \$130.00 for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h))				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	
Total claims	11 - 20 =	0	x \$ 50.00	\$ 0.00	
Independent claims	3 - 3 =	0	x \$200.00	\$ 0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$360.00	\$ 360.00	
TOTAL OF ABOVE CALCULATIONS =				\$ 1260.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees above are reduced by 1/2.				\$	
SUBTOTAL =				\$ 1260.00	
Processing fee of \$130.00 for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
TOTAL NATIONAL FEE =				\$ 1260.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$ 0.00	
TOTAL FEES ENCLOSED =				\$ 1260.00	
				Amount to be refunded:	\$
				Amount to be charged:	\$

IAP2 Rec'd PCT/PTO 29 SEP 2006

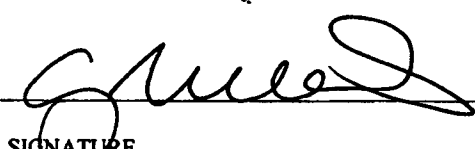
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.7) 10/594969 <small>Unassigned</small>		INTERNATIONAL APPLICATION NO. PCT/JP2005/006357	ATTORNEY'S DOCKET NUMBER 68600.000002
<p>a. <input checked="" type="checkbox"/> A check in the amount of <u>\$1260.00</u> to cover the above fees is enclosed.</p> <p>b. <input type="checkbox"/> Please charge Deposit Account No. <u>50-0206</u> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit to Deposit Account No. <u>50-0206</u>. A duplicate copy of this sheet is enclosed.</p> <p>d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.</p>			
<p>NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</p>			
<p>SEND ALL CORRESPONDENCE TO:</p> <p>CUSTOMER NO. 21967 Intellectual Property Department Hunton & Williams LLP 1900 K Street, N.W.; Suite 1200 Washington, DC 20006-1109 (202) 955-1500 (telephone) (202) 778-2201 (facsimile)</p>		<p> SIGNATURE</p> <p>Christopher J. Nichols, Ph.D. NAME</p> <p>55,984 REGISTRATION NUMBER</p> <p>DATE September 29, 2006</p>	

Exhibit C
USPTO Patent Term Adjustment History

10/594,969	ADIPONECTIN EXPRESSION-INDUCING AGENTS AND USES THEREOF	08-12-2010::16:36:29
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Transaction History

Date	Transaction Description
06-25-2010	Sequence Moved to Public Database
06-22-2010	Recordation of Patent Grant Mailed
06-02-2010	Issue Notification Mailed
06-22-2010	Patent Issue Date Used in PTA Calculation
05-04-2010	Dispatch to FDC
05-04-2010	Dispatch to FDC
04-30-2010	Application Is Considered Ready for Issue
04-30-2010	Mail Response to 312 Amendment (PTO-271)
04-29-2010	Response to Amendment under Rule 312
04-19-2010	Amendment after Notice of Allowance (Rule 312)
04-19-2010	Issue Fee Payment Verified
04-19-2010	Issue Fee Payment Received
02-19-2010	Sequence Forwarded to Pubs on Tape
01-26-2010	Mail Examiner's Amendment
01-26-2010	Mail Notice of Allowance
01-15-2010	Document Verification
01-15-2010	Notice of Allowance Data Verification Completed
01-15-2010	Case Docketed to Examiner in GAU
01-04-2010	Examiner's Amendment Communication
08-04-2009	Information Disclosure Statement (IDS) Filed
08-04-2009	Information Disclosure Statement considered
10-26-2009	Date Forwarded to Examiner
09-28-2009	Response after Non-Final Action
09-28-2009	Request for Extension of Time - Granted
08-04-2009	Information Disclosure Statement (IDS) Filed
05-26-2009	Mail Non-Final Rejection
05-11-2009	Non-Final Rejection
09-29-2006	Information Disclosure Statement considered
12-12-2006	Information Disclosure Statement considered
01-24-2007	Information Disclosure Statement considered
04-16-2009	Date Forwarded to Examiner
04-02-2009	Response to Election / Restriction Filed
04-02-2009	Request for Extension of Time - Granted
10-10-2008	Mail Restriction Requirement
09-29-2008	Requirement for Restriction / Election
04-08-2008	Case Docketed to Examiner in GAU
08-30-2007	PG-Pub Issue Notification
07-19-2007	Case Docketed to Examiner in GAU
05-22-2007	Corrected filing receipt
07-06-2007	Transfer Inquiry to GAU
01-24-2007	Information Disclosure Statement (IDS) Filed
12-12-2006	Information Disclosure Statement (IDS) Filed

09-29-2006	Information Disclosure Statement (IDS) Filed
06-11-2007	IFW TSS Processing by Tech Center Complete
01-24-2007	Reference capture on IDS
01-24-2007	Information Disclosure Statement (IDS) Filed
12-12-2006	Information Disclosure Statement (IDS) Filed
09-29-2006	Preliminary Amendment
10-27-2006	New or Additional Drawing Filed
09-29-2006	Preliminary Amendment
09-29-2006	Information Disclosure Statement (IDS) Filed
09-29-2006	Request for Foreign Priority (Priority Papers May Be Included)
05-15-2007	Application Dispatched from OIPE
03-14-2007	371 Completion Date
05-09-2007	Sent to Classification Contractor
05-09-2007	Notice of DO/EO Acceptance Mailed
10-15-2006	Cleared by OIPE CSR
10-15-2006	IFW Scan & PACR Auto Security Review
10-13-2006	CRF Is Good Technically / Entered into Database
09-29-2006	CRF Disk Has Been Received by Preexam / Group / PCT
09-29-2006	Initial Exam Team nn

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Exhibit D
USPTO Transaction History

10/594,969

ADIPONECTIN EXPRESSION-INDUCING AGENTS AND USES THEREOF

08-12-

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Transaction History

Date	Transaction Description
06-25-2010	Sequence Moved to Public Database
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05-26-2009	Mail Non-Final Rejection
05-11-2009	Non-Final Rejection
09-29-2006	Information Disclosure Statement considered
12-12-2006	Information Disclosure Statement considered
01-24-2007	Information Disclosure Statement considered
04-16-2009	Date Forwarded to Examiner
04-02-2009	Response to Election / Restriction Filed
04-02-2009	Request for Extension of Time - Granted
10-10-2008	Mail Restriction Requirement
09-29-2008	Requirement for Restriction / Election
04-08-2008	Case Docketed to Examiner in GAU
08-30-2007	PG-Pub Issue Notification
07-19-2007	Case Docketed to Examiner in GAU
05-22-2007	Corrected filing receipt
07-06-2007	Transfer Inquiry to GAU
01-24-2007	Information Disclosure Statement (IDS) Filed
12-12-2006	Information Disclosure Statement (IDS) Filed

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09-29-2006	Preliminary Amendment
09-29-2006	Information Disclosure Statement (IDS) Filed
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05-15-2007	Application Dispatched from OIPE
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09-29-2006	Initial Exam Team nn

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